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Cardiac Involvement with Parasitic Infections

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INTRODUCTION

Human parasitic infections are ubiquitous and affect a substantial number of individuals worldwide. Protozoan and helminth parasites can lead to a wide array of clinical manifestations during their migration inside the human body or when they reach their end organ of infection. Moreover, some parasitic infections are associated with significant morbidity and mortality in areas of high endemicity.

The heart and the lungs are the thoracic organs more frequently affected by parasitic infections. The involvement of the heart may be part of a more generalized illness, as is the case with human African trypanosomiasis (HAT). In other situations, parasitic infections may have more direct effects on various structures of the heart (myocardium, pericardium, endocardium, or the cardiac vasculature). The involvement of the myocardium may lead to myocarditis or different types of cardiomyopathies (i.e., dilated or restrictive). When the pericardium is affected, it may lead to pericarditis, pericardial effusion, cardiac tamponade, or constrictive pericarditis. Some parasitic infections, such as schistosomiasis, may cause pulmonary hypertension in many developing tropical and subtropical settings. Latent parasitic infections may also reactivate and manifest as systemic disease, often ultimately affecting the heart, in immunosuppressive states such as organ transplantation, the use of immunosuppressive agents, or HIV/AIDS. Due to growing migration, population displacement, and travel, clinicians anywhere around the globe must be aware of the potential cardiac manifestations of parasitic diseases. In this regard, Chagas' cardiomyopathy is the hallmark of a disease that is currently considered a global parasitic disease (106).

In this review, we present an overview of the most frequently identified parasitic infections that affect the heart. For each topic we present a discussion of the epidemiology, pathogenesis, clinical manifestations, and treatment. Table 1 provides a summary of these data. We dedicated most of our paper to the discussion of trypanosomiasis, both American (Chagas' disease) and African (sleeping sickness), since they constitute the most relevant parasitic infections involving the heart.

PARASITES THAT PREFERENTIALLY INVOLVE THE MYOCARDIUM OR CAUSE PANCARDITIS

Trypanosomes

***Trypanosoma cruzi* (Chagas' disease).** Chagas' disease, also known as American trypanosomiasis, is a zoonotic tropical disease caused by the flagellate protozoan parasite *Trypanosoma cruzi*. Most infections occur through vector-borne transmission by triatomine insects in areas of endemicity but can also occur through blood transfusion or organ transplantation, vertically from mother to infant, and, more rarely, by ingestion of food or liquid contaminated with *T. cruzi* or accidents among laboratory personnel who work with live parasites (193). Vector-borne transmission involves the transmission of the infective form of the parasite (the metacyclic trypomastigotes) to humans by the excreta of the triatomine insect through mucous membranes or through breaks in the skin. Trypomastigotes then invade local host cells, where they differentiate into amastigotes and multiply within the cell. When the cell is swollen with amastigotes, they transform back into trypomastigotes by growing flagellae. The trypomastigotes lyse the cells, invade adjacent tissues, and spread via the lymphatics and bloodstream to distant sites. The cycle is completed when a reduviid bug becomes infected by ingesting blood from an infected host (193). A minority of patients will develop an acute syndrome of 4 to 8 weeks' duration, which invariably involves prolonged fever in addition to a variable constellation of symptoms, which include inflammation at the portal of entry, subcutaneous edema (localized or generalized), lymphadenopathy, hepatosplenomegaly, myocarditis, and, more rarely, meningoencephalitis (169, 253, 254). The manifestations of the acute phase resolve spontaneously for the vast majority of individuals even if the infection is not treated with an antiparasitic drug. About 60 to 70% of these patients will never develop clinically apparent diseases. They remain asymptomatic and infected life long, being recognized only if serological tests are performed (the so-called indeterminate form of chronic Chagas' disease). Roughly 30 to 40% of infected patients will subsequently develop the cardiac and/or digestive (megaesophagus and megacolon) form of chronic Chagas' disease, usually 10 to 30 years after the initial infection (169, 254).

(i) Epidemiology. *Trypanosoma cruzi* is endemic in South America, Central America, and parts of North America (Southern United States and Mexico). Historically, the disease disproportionately affected the poor because the transmission of *T. cruzi* infection occurred mainly in rural areas where humans live in poor-quality houses and in close contact with potential vectors. However, rural-to-urban and international migrations have changed the epidemiology of Chagas' disease, affecting periurban areas, urban areas, areas of endemicity, and areas of nonendemicity alike (222). As a result of these dynamic changes in the population and the coordinated efforts of countries where disease is endemic to interrupt vectorial and trans-

TABLE 1. Epidemiology, pathogenesis, clinical manifestations, and treatment of parasitic infections that affect the heart

Parasitic infection	Causative organism	Geographic distribution	Mode of transmission	Heart involvement	Cardiac manifestation(s)[a]	Etiological treatment
Chagas' disease (American trypanosomiasis)	*Trypanosoma cruzi*	South and Central America, Mexico, and Southern United States	Vector-borne; transfusional congenital organ transplant; food borne; accidental	Myocarditis and pericarditis (acute phase); cardiomyopathy (chronic phase)	ECG changes (sinus tachycardia, first-degree atrioventricular block, low Q-R-S voltage, primary T-wave changes); cardiomegaly; pericardial effusion; heart failure; sinus node dysfunction; atrioventricular and intraventricular blocks; ventricular arrhythmias; apical aneurysm; heart failure; sudden cardiac death	Benznidazole or nifurtimox (optional, because benefit is not well established)
African trypanosomiasis (sleeping sickness)	*T. b. gambiense*, *T. b. rhodesiense*	West and Central Africa, East and Southern Africa	Vector borne; others (transfusional, congenital, and accidental are rare)	Pancarditis (within months or years after infection); pancarditis (within weeks after infection)	ECG changes (ST-T changes, low Q-R-S voltage, Q-Tc prolongation, P-R segment depression); cardiomegaly; pericardial effusion; heart failure (mild); ECG changes; cardiomegaly; pericardial effusion; heart failure (moderate to severe)	Pentamidine (early stage); melarsoprol or eflornithine (late stage); suramin (early stage); melarsoprol (late stage)
Toxoplasmosis	*Toxoplasma gondii*	Worldwide	Fecal-oral; food-borne; congenital; transfusional; organ transplant	Myocarditis and pericarditis (rare in immunocompetent individuals; more common in immunocompromised infected persons)	ECG changes; cardiomegaly; pericardial effusion; constrictive pericarditis; arrhythmias; heart failure	Pyrimethamine + sulfadiazine or pyrimethamine + clindamycin (plus folinic acid); pyrimethamine (+ azithromycin or atovaquone) for intolerant patients; pyrimethamine + sulfadiazine (pregnancy)
Cysticercosis	*Taenia solium*	Worldwide (rural areas in developing countries)	Fecal-oral	Myocarditis (very rare)	Arrhythmias; conduction abnormalities	Albendazole or praziquantel (optional because their role is still unclear)
Trichinellosis	*Trichinella spiralis*	Worldwide	Food-borne	Myocarditis and pericarditis	Arrhythmias; pericardial effusion	Albendazole or mebendazole (in conjunction with steroids for severe cases)
Amebiasis	*Entamoeba histolytica*	Worldwide (developing countries in the tropics)	Fecal-oral	Pericarditis	ECG changes; pericardial effusion; cardiac tamponade	Metronidazole
Echinococcosis	*Echinococcus granulosus*	Worldwide (rural areas)	Fecal-oral	Pericarditis; cysts anywhere in the heart	Arrhythmias; myocardial infarction; cardiac tamponade; pulmonary hypertension; sudden cardiac death	Albendazole or mebendazole

[a] Q-R-S and ST-T, Q-R-S and ST-T intervals of the ECG; Q-Tc, the Q-T interval of the ECG corrected for heart rate.

fusional transmission, the prevalence and incidence of the disease are constantly changing. In the 1980s the overall prevalence of *T. cruzi* infection was estimated to reach 17 million cases in 18 countries where disease is endemic, with 100 million people at risk (222). Multinational vector control programs and compulsory blood bank screening achieved enormous success in the 1990s, decreasing the incidence of new infections (700,000 cases per year in 1983) by 70% and the number of annual deaths by approximately 50% for the whole continent and eradicating the transmission of *T. cruzi* by the main domiciliary vector species, *Triatoma infestans*, from three of the countries where *T. cruzi* is endemic (Uruguay in 1997, Chile in 1999, and Brazil in 2006) (209, 222). According to the most recent estimates, there are currently 7.6 million people infected with *T. cruzi* in Latin America (239). Although precise figures documenting the total burden of cardiac involvement with *T. cruzi* are not available, it can be assumed that 20 to 30% of the 7.6 million infected individuals are or will potentially be developing chronic cardiac lesions. Chagas' cardiomyopathy, in turn, is thought to represent the principal cause of cardiac morbidity and mortality among young adults in countries where *T. cruzi* is endemic and has been estimated to result in at least 21,000 deaths each year (222, 268, 344). Additionally, because of the constant influx of immigrants from countries where the disease is endemic, Chagas' disease is becoming an important health issue in North America (United States and Canada) and many parts of Europe, where a growing number of individuals are suspected to be infected (e.g., 300,000 individuals in the United States and 48,000 to 67,000 individuals in Spain) (27, 113).

(ii) Pathology and pathophysiology of acute myocarditis and chronic cardiomyopathy. Initially, the abundance of parasites associated with the acute phase of *T. cruzi* infection argued in favor of the parasite's direct implication in the tissue damage and myocarditis observed during this stage of the disease. Shortly afterwards, a demonstration of myocytolysis of nonparasitized cardiomyocytes led to the implication of parasite-directed cellular immune-mediated inflammatory damage (14). This immune-mediated damage, associated with large numbers of amastigotes in cardiac myocytes, translates into the hyaline degeneration of muscle fibers, the coagulation necrosis of myocytes and surrounding tissues, as well as the involvement of the epicardium and pericardium (14, 193). Cellular and, possibly, humoral immune responses elicited by the parasite eventually control the acute infection but fail to completely eliminate the parasite. A variably long asymptomatic phase then ensues, where factors such as the parasite strain, the parasite load during the acute phase, the quality of the immune response, and the presence or absence of reinfection all might influence the course of chronic disease (52, 199). Regarding the pathogenesis of the interstitial fibrosis, myocytolysis, and ongoing lymphocytic infiltration observed for the chronic phase of Chagas' disease, the paucity of parasites in cardiac tissue probably reflects the use of insensitive histological techniques in past decades. In recent years, more powerful and sensitive methods of parasite detection, such as immunohistochemistry and PCR, have demonstrated a higher frequency of *T. cruzi* antigens or parasite DNA in chronic lesions (134, 148). The spectrum of outcomes for patients infected with *T. cruzi* is varied and probably stems from intrinsic genetic differences of both the parasite and the host and perhaps even the likelihood of ongoing infection in areas where the disease is highly endemic. Evidence exists for multiple hypotheses to explain the etiology of chronic cardiac lesions that implicate the parasite directly, the immune reaction to the parasite, and autoimmunity elicited either directly by the parasite (mimicry) or indirectly (bystander activation) (98). The products of these lesions are various degrees of necrosis, neuronal damage, microvascular damage, and fibrosis. The contributing role of each mechanism to the pathogenesis of Chagas' cardiomyopathy is a whole other topic of debate (201).

There is evidence for both functional and anatomical parasympathetic neuronal damage in Chagasic patients (10, 184). Patients with Chagas' disease lack the tonic inhibitory parasympathetic action on the sinus node and, thus, the chronotropic mechanism to respond to changes in blood pressure or venous return (10). Neuronal loss is thought to occur during the acute stage of the disease; the extent of neuronal damage, however, does not correlate with disease stage (10, 184, 200). Therefore, despite possible contributions of parasympathetic impairment to the impact of Chagas' heart disease (e.g., increasing vulnerability to malignant arrhythmias and sudden death or accentuating existing contraction abnormalities that can culminate in chamber dilatation), cardiac dysautonomia is unlikely to explain the main pathogenic mechanism underlying Chagas' cardiomyopathy (201).

In addition to the neuronal damage, microcirculatory changes leading to ischemia have also been implicated in the pathogenesis of chronic Chagas' cardiomyopathy. A diffuse collapse of intramyocardial arterioles in the hearts of chronically infected patients has been observed (201). Occlusive platelet thrombi in small epicardial and intramural coronary arteries and increased production of cytokines and mediators that promote vasospasm and platelet aggregation have been demonstrated with experimental models of Chagas' disease (228, 283, 314). Clinically, despite consistently normal epicardial coronary arteries upon coronary angiography, reversible perfusion defects upon stress-induced myocardial perfusion scintigraphy that correlate with ischemia and abnormal coronary flow regulation have been shown for patients with chronic Chagas' cardiomyopathy (202, 204).

As mentioned above, tissue damage caused directly by the parasite or, more likely, by the immune response elicited by it has been postulated to underlie and potentiate the aggression to cardiac myocytes and neurons. The inflammatory infiltrate in chronic Chagas' cardiomyopathy involves a predominance of macrophages, $CD8^+$ and $CD4^+$ lymphocytes (in a 2:1 ratio), and in some instances has been shown to correlate with more advanced stages of the disease (74, 135). The persistence of parasites and antigens is thought to be involved in the recruitment of *T. cruzi*-specific $CD8^+$ T lymphocytes, which predominate in the myocardial infiltrate in cases of chronic Chagas' myocarditis (132, 133). The cytokine profile associated with this myocarditis is also shifted toward Th1 cytokines, so elevated gamma interferon (IFN-γ) levels and decreased interleukin-10 (IL-10) levels may potentially perpetuate an existent, ongoing inflammatory process (117, 317). However, the exact mechanism responsible for the turning point from immunoprotection to immune-mediated aggression leading to irreversible tissue damage remains elusive: not only is parasite persis-

tence true for both symptomatic and asymptomatic patients, but the presence of the parasite in heart tissue does not always correlate with inflammation (236, 243).

Autoimmunity has also been postulated to be a plausible etiology for the chronic myocarditis observed for *T. cruzi*-infected patients. Several *T. cruzi* antigens that cross-react with cardiac and noncardiac host components have been identified, but only some have been shown to have functional activity (201). Among these, attention has focused on antibodies that cross-react with cardiac myosin and the immunodominant *T. cruzi* antigen B13 initially, because they were detected in 100% of patients with chronic Chagas' cardiomyopathy, in contrast to 14% of asymptomatic infected individuals (76), and later because T-cell clones derived from lesions of patients with chronic Chagas' cardiomyopathy were found to be simultaneously reactive to cardiac myosin heavy chain and the B13 *T. cruzi* protein (75). Opponents of the molecular mimicry theory with specific relevance to anti-B13-cardiac myosin cross-reactive antibodies and derived cellular autoimmunity contend that these antibodies do not bind to intact myocytes, are not unique to *T. cruzi* infection, and are present in asymptomatic patients without heart lesions and that myosin autoimmunity is not essential for cardiac inflammation in experimental models (158, 174, 232). Arguing against autoimmunity developing as a result of parasite-specific immune responses, antigen exposure after tissue damage may also sensitize autoreactive T cells to self-antigens given a proinflammatory environment (98, 313). The question, therefore, is not whether autoimmunity is present but whether it is a primary cause of or merely a contributing factor to the pathogenesis of chronic Chagas' myocarditis. As proposed by Kierszenbaum, this question remains to be answered by experiments that prove a clear association between the development of similar cardiac lesions with the transfer of autoantibodies and/or autoreactive cells to susceptible hosts (158).

To synthesize, although the effects of both autonomic and microvascular disturbances in Chagas' cardiomyopathy may play an important role in potentiating and perpetuating cardiac muscle damage, persistent inflammation in the setting of continuous antigenic stimulation is perhaps the common pathway for tissue damage. Multiple mechanisms seem to explain this chronic inflammation (mainly antiparasite immunity and, possibly, autoimmunity), which are not necessarily mutually exclusive. The course of progression to chronic Chagas' cardiomyopathy and other forms of the disease was suggested to be related to genetic properties of both the host and the parasite (13). However, the molecular mechanisms underlying tissue tropism and the initial trigger or determinant of the course of chronic disease are not yet known.

(iii) Clinical manifestations of heart involvement. *(a) Myocarditis during the acute phase*. Acute myocarditis as evidenced by autopsy studies probably happens in close to 100% of patients with acute Chagas' disease (169, 245). However, there is an enormous discrepancy between autopsy findings and clinical data: first because acute infection is asymptomatic for approximately 90 to 95% of cases and second because even for symptomatic patients, acute Chagasic myocarditis is diagnosed for only 1 to 40% of them (253, 281, 344). Findings upon cardiac auscultation may include tachycardia (not always proportional to the degree of fever), cardiac murmurs, and muffled heart sounds (253, 271). The principal electrocardiographic (ECG) alterations are first-degree atrioventricular (AV) block, low Q-R-S (Q-R-S interval of the ECG) voltage, and primary T-wave changes (245, 253, 271). A chest radiograph may show variable degrees of cardiomegaly, and pericardial effusion is the most frequently reported echocardiographic abnormality (245, 253). Death in the acute phase occurs occasionally (for 5 to 10% of symptomatic patients) as a result of congestive heart failure (due to severe myocarditis) and/or meningoencephalitis (169, 245, 253, 289). After the acute phase most patients return to a normal or near-normal myocardial status, but some patients (30%) then chronically develop fibrosing myocarditis (261).

Among immunosuppressed hosts such as HIV-infected individuals and transplant recipients, reactivation of infection and *de novo* infection (including transmission with transplanted organs among transplant patients) have been reported (22, 104). With reactivation in HIV-positive patients, myocarditis has been reported for up to 45% of cases (104). Reactivation of Chagas' disease among heart transplant patients has been estimated to occur in approximately 30% of cases (105). However, not all these cases are accompanied by florid symptoms or diagnosed by endomyocardial biopsy, and therefore, the true incidence of myocarditis with reactivation is difficult to estimate. Acute *T. cruzi* infection can also result as a consequence of donor-related transmission, which has been reported after kidney, heart, liver, and multiorgan transplants (206). Involvement in this setting can range from asymptomatic parasitemia that easily responds to treatment without further complications to severe, fulminant disease despite therapy (including death directly attributable to Chagasic myocarditis) (206). In congenitally infected infants, the most common symptoms, which may be apparent at birth or develop within weeks after delivery, are hipotonicity, fever, hepatosplenomegaly, and anemia. Other findings include prematurity and low birth weight (36, 107). *In utero* infections are also associated with abortion and placentitis. Serious manifestations, including myocarditis, meningoencephalitis, and pneumonitis, are uncommon but carry a high risk of death (323).

(b) Chronic Chagas' cardiomyopathy. Cardiac involvement is the most frequent and most severe manifestation of chronic Chagas' disease (269). Transition from the indeterminate form to the cardiac form of chronic Chagas' disease is usually manifested by the appearance of ECG changes such as incomplete or complete right bundle branch block (RBBB), left anterior fascicular block (LAFB), minimal ST-T (ST-to-T interval of the ECG) changes, and monomorphic premature ventricular contractions (PVCs), mostly in asymptomatic or oligosymptomatic patients (169, 194). As the disease advances, associated intraventricular conduction defects (usually RBBB with LAFB), polymorphic PVCs (Fig. 1), bradyarrhythmias, high-grade atrioventricular blocks, Q waves, nonsustained or sustained ventricular tachycardia, and, ultimately, atrial flutter or fibrillation may ensue (Table 2). Symptoms like palpitations, atypical chest pain, presyncope, syncope, dyspnea upon exertion, and edema are usually observed throughout the course of chronic Chagas' cardiomyopathy (CCC) (2, 169, 237, 268, 270) (Table 2). Findings upon physical examination vary according to the stage of the disease and the presence of conduction system abnormalities. These findings include cardiac rhythm

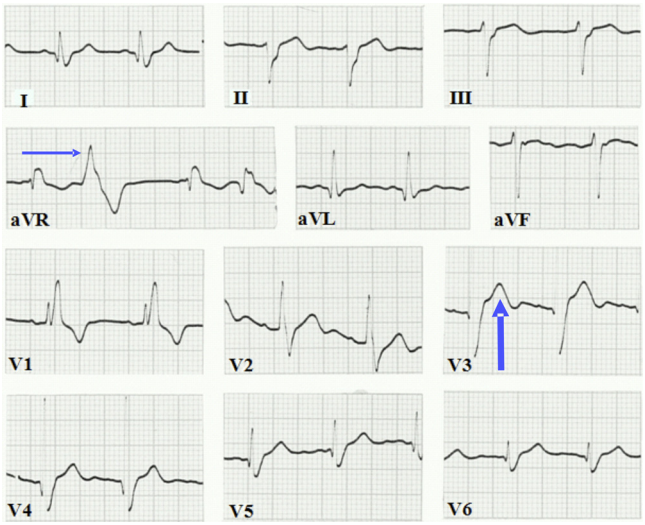

FIG. 1. ECG of a patient with CCC showing the three most typical alterations: right bundle branch block, left anterior fascicular block (large blue arrow), and ventricular extrasystole (small blue arrow). aVR, aVL, and aVF are the right lead-augmented vector, left lead-augmented vector, and lead-augmented vector foot, respectively, of the 12-lead ECG.

irregularities, a displaced point of maximal impulse, gallop rhythms, a loud second heart sound implying pulmonary hypertension, mitral or tricuspid regurgitation murmurs, an increase in the systemic venous pressure with liver enlargement and edema, and a borderline low systolic blood pressure with a reduced radial pulse implying systolic dysfunction (169). Upon echocardiogram, diastolic dysfunction usually precedes systolic dysfunction, potentially allowing the early detection of cardiac involvement in Chagas' disease (216). Characteristic echocardiographic findings include apical aneurysms (Fig. 2), which are reported for 8.5 to 55% of cases (depending on the stage of the disease and the method of detection, i.e., if postmortem or at echocardiography or angiography); segmental left ventricular (LV) contractile abnormalities (more commonly at the posteroinferior wall); and reduced LV systolic function (2). Echocardiographic evidence of impaired LV function, as characterized by increased LV systolic dimension, reduced LV ejection fraction, or the presence of segmental or global LV wall motion abnormality and/or an LV aneurysm, is the most common and consistent independent predictor of death (269). Other important clinical and noninvasive adverse prognostic indicators, which not surprisingly reflect and parallel the degree of myocardial dysfunction, include advanced functional class (New York Heart Association [NYHA] classification III/IV), cardiomegaly, and nonsustained ventricular tachycardia upon 24-h ECG monitoring (269).

The clinical course of CCC is diverse and difficult to predict, with some patients remaining asymptomatic life long despite electrocardiographic and/or echocardiographic evidence of the disease, some presenting with signs, symptoms, and complications of progressive heart failure or advanced cardiac arrhythmias, and others dying unexpectedly without prior symptoms (269). Currently, several staging systems are available. These staging systems can help to identify patients at different degrees of risk, facilitate choices among treatment alternatives, and aid patient counseling. Most systems classify patients into four or five stages based on their functional capacity, ECG findings, and the presence or absence of heart enlargement and/or systolic dysfunction upon echocardiogram (2, 57, 141, 167, 217) (Table 3). The progression of disease to more advanced stages has been estimated to occur for 10% of patients over a follow-up period of 3 to 10 years (101). Another important aspect of staging is derived from its prognostic information: the rate of mortality for individuals at early stages of CCC is not significantly different from that of the general population (101). However, the life expectancy of patients with symptomatic and advanced CCC stages (involving systolic dysfunction and/or cardiomegaly) is less than 30% at 5 years (58, 101), and their overall prognosis is worse than that of patients with dilated cardiomyopathies of other etiologies (108). Systemic and pulmonary embolisms arising from mural thrombi in the cardiac chambers are relatively frequent (289). Although the brain is by far the most common clinically recognized site of embolisms (followed by limbs and lungs), at necropsy, embolisms are found more frequently in the lungs, kidneys, and spleen. Chagas' disease is an independent risk factor for stroke in areas where the disease is endemic (56). Mortality in CCC is due to sudden cardiac arrest in 55 to 65% of patients, congestive heart failure in 25 to 30% of patients, and thromboembolic phenomena in 10 to 15% of patients (270).

TABLE 2. Hallmarks of chronic Chagas' cardiomyopathy[a]

Hallmark of CCC
Arrhythmias
Ventricular extrasystoles
Nonsustained and sustained ventricular tachycardia
Bradyarrhythmias
Ventricular fibrillation
Atrial fibrillation/flutter
Conduction abnormalities
Sick sinus syndrome
Complete and incomplete right bundle branch block
Left anterior fascicle block
Bifascicular and trifascicular blocks
1st-, 2nd-, and 3rd-degree AV blocks
Thromboembolic phenomena
Brain (most frequent)
Lungs, kidneys, spleen
Cardiac failure
Diastolic dysfunction initially
Isolated left heart failure in the early stages of cardiac decompensation
Biventricular with a predominance of right-sided failure in advanced stages
Apical aneurysm
Found in 52% of autopsy series
More frequent in men
80% in the LV apex
Sudden death secondary to:
Ventricular fibrillation (most frequent)
Bradyarrhythmias
Rupture of apical aneurysm (exceptional)

[a] See references 15, 179, 244, and 274.

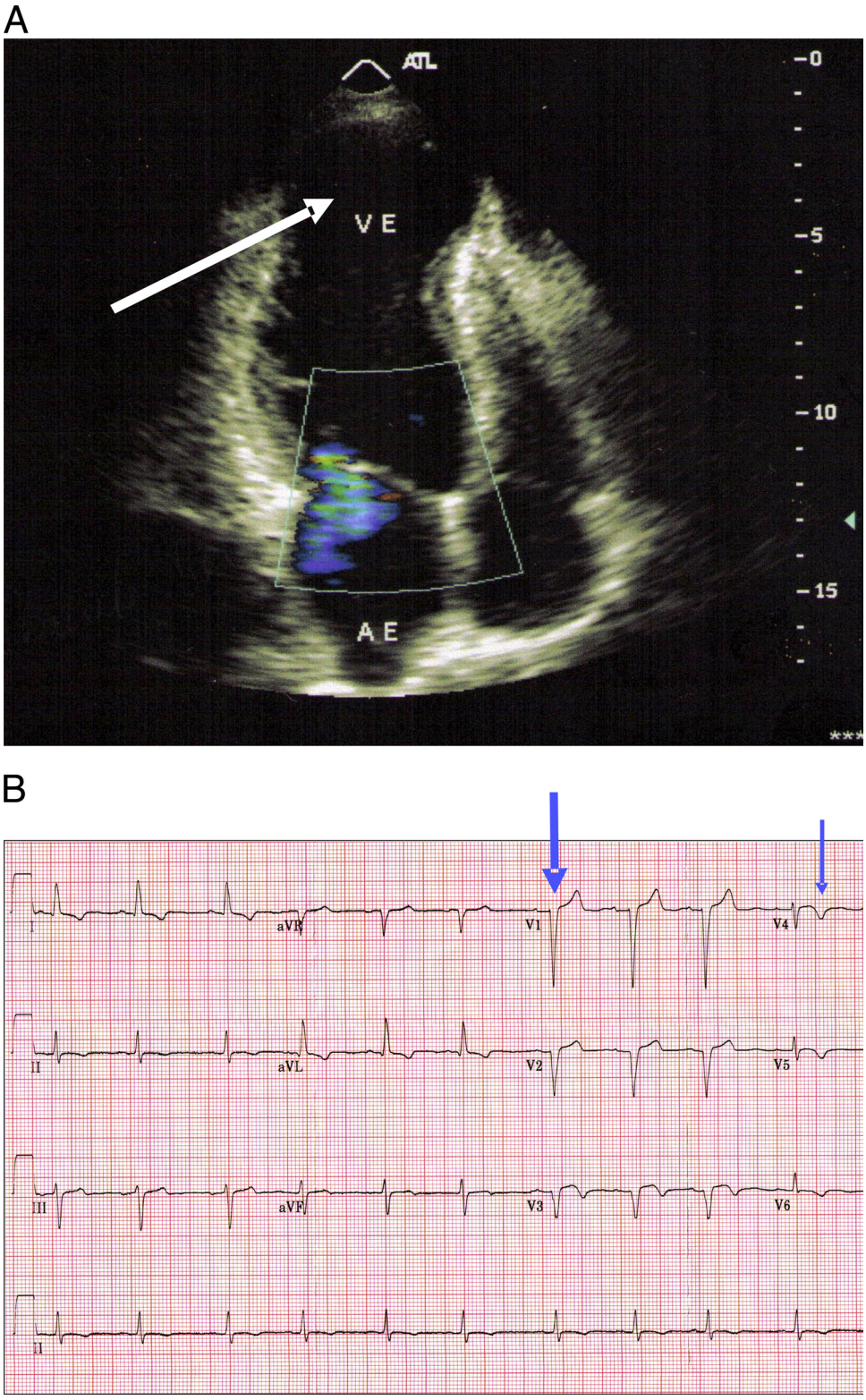

FIG. 2. (A) 2D color Doppler echocardiography of a patient with CCC showing an apical left ventricular aneurysm (large white arrow) (AE is the left atrium, and VE is the left ventricle). ATL refers to the video output of the echocardiographic system of three-dimensional transesophageal echocardiography (Apogee CX 200; ATL Corp.). (B) ECG of the same patient showing anteroseptal Q waves (large blue arrow) and primary T-wave changes (mimicking coronary artery disease) (small blue arrow).

TABLE 3. Summary of classification schemes/staging systems for heart involvement in chronic Chagas' disease[a]

Classification scheme or staging system (reference)
First stage, indeterminate form
No evidence of heart involvement by:
ECG and CXR (stage 0 KC) (177)
ECG, echocardiogram, and signs of CHF (stage IA MLAC) (69)
ECG, echocardiogram, CXR, and NYHA functional class (stage A-ACC/AHA) (15, 151)
Second stage: CCC without signs or symptoms of heart failure
Evidence of structural heart disease by:
ECG +/− CXR (stage I-II KC) (177)
ECG +/− echocardiogram (stage A-B2 BCC) (3)
Echocardiogram +/− ECG (stage IB-II MLAC) (69)
ECG (stage B A-ACC/AHA) (15, 151)
Third stage: compensated CCC
Takes into account symptoms
Compensated CHF (stage C BCC) (3)
NYHA II–III (stage C A-ACC/AHA) (15, 151)
Fourth stage: overt, refractory, or advanced CCC
Includes:
Stage III from the KC and the MLAC (69, 177)
Stage D from the BCC and the A-ACC/AHA classification (3, 15, 151)

[a] According to the modified Kuschnir classification (KC), the Brazilian Consensus classification (BCC), the modified Los Andes classification (MLAC), and the classification incorporating American College of Cardiology/American Heart Association (ACC/AHA) staging (A-AAA/AHA) (3, 15, 69, 151, 177). CXR, chest radiograph; CHF, congestive heart failure; NYHA, New York Heart Association.

(iv) Diagnosis. Diagnosis of acute Chagas' myocarditis relies on the demonstration of the parasite and/or anti-*T. cruzi* IgM in a patient with the correct epidemiological background and clinical picture. IgM serology assays are not widely available in developing countries and not standardized, so diagnosis is usually performed by visualizing the trypomastigotes in fresh blood smears, thick drop preparations, or buffy coat smears (159, 169). The level of parasitemia diminishes to almost undetectable levels by the 6th to 10th weeks of infection, making parasite identification in peripheral blood extremely difficult at this time (169). Diagnosis could also be attempted by hemoculture on specialized medium (which has improved sensitivity over direct examination) or xenodiagnosis (which involves detecting the parasite by infecting laboratory-reared triatomine bugs directly or indirectly with the patient's blood) (159, 169, 226). However, even considering only congenital Chagas' disease, hemoculture is rarely performed for the diagnosis of acute infection since it requires a specialized laboratory and trained personnel and is usually not widely available. Indirect parasitological tests are of limited value in the diagnosis of acute Chagas' disease, as they can take more than 1 month to obtain results (retarding the beginning of trypanocidal therapy).

A diagnosis of CCC should be suspected for young or middle-aged patients who present with a segmental or dilated cardiomyopathy of unknown etiology if within areas of endemicity or within the right epidemiological context. It should be remembered that CCC presents years after the initial infection, and therefore, patients who migrated to areas where the disease is not endemic are still at risk of developing cardiac compromise. Given the low and probably intermittent parasitemia in the chronic phase, diagnosis relies on serological methods by detecting IgG that binds to *T. cruzi* antigens (159). Enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF), and indirect hemagglutination (IHA) methods are most commonly employed (28, 159, 344). Two positive tests using any of the three conventional techniques are recommended for a final diagnosis (344). Identification of the parasite by hemoculture or xenodiagnosis in the chronic phase of the disease is hampered by the low sensitivity of the methods, which is dependent directly on the level of parasitemia. However, these methods may have a role in confirming the diagnosis in rare cases of serologically doubtful results or in evaluating treatment failures at specialized centers (252).

PCR-based methods using one of two target sequences (the variable region of the minicircle kinetoplast DNA and a 195-bp reiterated DNA sequence of the parasite) have achieved higher sensitivities than those of xenodiagnosis and hemoculture (60, 285, 344). The major problems with PCR-based techniques are the lack of standardization and commercial availability of assays for *T. cruzi*, the high level of complexity required, and the reliance of their sensitivity on the level of parasitemia (which is low, by definition, in chronic disease) (344). PCR is therefore still considered among nonconventional methods and is recommended only as an adjunct in specialized centers to confirm parasitemia in congenital *T. cruzi* infection (since in this context, its sensitivity seems to be greater than that of microscopic examination) or for the evaluation of antiparasitic drug therapy (49, 344). However, a single or even repeated negative posttreatment PCR results do not necessarily mean parasitological cure. The negative results are indicative only of the absence of parasite DNA at those moments. The value of PCR lies mainly in the positive results that they yield, which usually reflect treatment failure (49, 344). Whether assessments of parasite load by quantitative real-time PCR will correlate with the impact of trypanocidal treatment on parasitological cure or resistance, as well as on disease evolution, should be a matter for further investigation.

The initial evaluation of the newly diagnosed patient with chronic *T. cruzi* infection includes a complete medical history and physical examination and a resting 12-lead electrocardiogram. Asymptomatic patients with a normal ECG have a favorable prognosis and should be followed up only annually or biannually (142). Patients with ECG changes consistent with CCC should undergo a routine cardiac evaluation, including ambulatory 24-h Holter monitoring (complemented with an exercise test whenever possible) to detect arrhythmias and assess functional capacity, chest radiography and two-dimensional (2D) echocardiography to assess ventricular function, and other cardiologic tests as indicated (28, 269). Based on the results of these tests, it is possible to stratify individual patients by risk and implement appropriate therapy (269).

(v) Treatment and preventive measures. *(a) Etiological treatment*. Only two drugs, benznidazole and nifurtimox, are recommended for the treatment of Chagas' disease (28, 344). Of the two, benznidazole (a nitroimidazole derivative) has been more extensively investigated in clinical studies and is better tolerated overall. Adverse reactions such as generalized or sometimes localized allergic dermatitis occur in approximately 20 to 30% of patients and consist of pruritic and nonbullous

polymorphous erythematous rashes, often followed by desquamation (61). Severe exfoliative dermatitis can occur and should lead to a prompt discontinuation of treatment (28, 61, 344). Another adverse effect that occurs in approximately 5 to 10% of patients, most commonly late in the treatment course, is a dose-dependent peripheral sensitive neuropathy affecting mainly the distal parts of the lower limbs; it also should prompt the cessation of treatment. Rare serious adverse events include leukopenia with granulocytopenia or agranulocytosis (sometimes followed by fever and tonsillitis) and thrombocytopenic purpura. Additional reported side effects include nausea, vomiting, anorexia, weight loss, insomnia, loss of taste, and onycholysis. Nifurtimox, a nitrofuran compound, has been associated with gastrointestinal side effects in 30 to 70% of patients as well as central and peripheral nervous system toxicity (28, 61, 278). Both compounds are better tolerated by children, allowing increased dosage regimens. Children should be treated with 10 mg/kg of body weight of benznidazole per day in two divided doses for 30 to 90 days or 15 to 20 mg/kg of nifurtimox per day in four divided doses for 90 to 120 days. Adults should be treated with 5 to 7 mg/kg of benznidazole per day in two divided doses for 30 to 60 days or 8 to 10 mg/kg of nifurtimox per day in three to four divided doses for 90 to 120 days (214).

Treatment has been recommended for all cases of acute and congenital infection, reactivated infection, and early chronic Chagas' disease (particularly children/adolescents $\leq$18 years of age) based on evidence of the shortening of the disease's clinical course, cure of infection, or reduction in numbers of parasites (28, 159, 193, 344). For infected adults without advanced cardiomyopathy up to the age of 50 years, etiological treatment should generally also be offered. The rationale for these recommendations stems from evidence of a slowing of the progression of cardiomyopathy (28, 334, 344). In a recent observational trial, 566 chronically infected adults (30 to 50 years of age) without heart failure were assigned, in alternating sequences, to benznidazole or no treatment (334). After a median follow-up period of 9.8 years, fewer treated patients had a progression of disease or developed ECG abnormalities. Negative seroconversion was more frequent for treated patients (334). Another recently published controlled study, including 111 patients (17 to 46 years of age) with chronic Chagas' disease and a normal electrocardiogram, showed similar favorable results with benznidazole over a mean follow-up period of 21 years (103). For those patients over the age of 50 years, etiological treatment is considered optional because of the lack of any available data. A multicenter, randomized, placebo-controlled trial of benznidazole enrolling 3,000 patients with mild to moderate CCC who were 18 to 75 years of age is currently under way and should help clarify treatment decisions for this population (203).

In contrast, etiological treatment is contraindicated during pregnancy and for patients with severe renal or hepatic insufficiency, and it should generally not be offered to patients with advanced Chagasic cardiomyopathy or megaesophagus with significant impairment of swallowing (28, 344). A more controversial issue is prophylactic treatment for transplant patients: some authors have recommended it for patients with Chagasic cardiomyopathy who undergo cardiac transplantation to prevent disease reactivation (206), while others recommend it for all infected donors pretransplant and for their respective recipients posttransplant (344). For chronic Chagas' disease, cure is documented when previously positive serological tests are negative, usually years or decades after treatment (344).

(b) Symptomatic treatment. Medical treatment of heart failure for patients with CCC should follow specific treatments targeted at each stage according to current guidelines for heart failure of other etiologies (141, 268). An important exception is the use of beta blockers, which should be used with caution for CCC due to a higher incidence of atrioventricular conduction defects and associated bradyarrhythmias (268). Cardiac transplantation has been performed with good results for patients with advanced CCC but may not be available or accessible in all countries where this disease is endemic (41, 79, 268). Although not tested in randomized controlled clinical trials, amiodarone has been associated with a survival advantage in case-control studies among patients with ventricular tachycardia and has therefore been proposed for the management of patients with sustained and nonsustained ventricular tachycardia (268, 270). However, treatment with amiodarone has been associated with pulmonary, cardiac, thyroid, liver, ocular, skin, central nervous system (CNS), and genitourinary toxicities, so treatment needs to be individualized (119). Pacemaker implantation is the recommended treatment for severe bradyarrhythmias and advanced conduction abnormalities. The roles of cardioverter-defibrillator implantation and cardiac resynchronization, however, are not well established for CCC (268, 270). Finally, anticoagulation has been advocated for patients with atrial fibrillation, previous thromboembolic phenomena, or an LV aneurysm with thrombus (268).

(c) Preventive measures. Most *T. cruzi* infections can be prevented by decreasing vectorial transmission, improving blood product screening, and detecting and treating transplacental transmission. Multinational programs involving countries where the disease is endemic have achieved enormous success in decreasing both the prevalence and incidence of Chagas' disease by following several operational stages. The tools for interrupting transmission are based on the implementation of vector control activities such as insecticide spraying, housing improvements, and education as well as the strengthening of the implementation of policy for use and screening of blood products for transfusion. Since the end of January 2007, the American Red Cross and other blood collection agencies in the United States began screening blood donations for antibodies to *T. cruzi* donations with the approved ELISA (referred to as universal testing). All initially reactive donations are retested in duplicate by using the same screening test; donations testing repeatedly reactive undergo confirmatory testing by the radioimmunoprecipitation assay (RIPA) (29). Continued surveillance is also important to consolidate and maintain the success achieved (222).

For persons traveling to areas of endemicity, compliance with general food and water precautions is advised to prevent the extremely rare occurrence of food-borne Chagas' disease. More importantly, travelers should avoid sleeping in poorly constructed houses or else consider sleeping in insecticide-impregnated bed nets. However, the protective efficacy of insecticide-treated materials in reducing Chagas' disease transmission and eliminating the vector population has yet to be demonstrated. Finally, no vaccine for Chagas' disease is available (131).

Other trypanosomes: *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. *T. b. rhodesiense* (in east and southern Africa) and *T. b. gambiense* (in west and central Africa) are the two flagellate parasites responsible for human African trypanosomiasis (HAT). The disease is caused by the bite of the tsetse fly (*Glossina*), which inoculates metacyclic trypanosomes that then multiply at the site of inoculation and disseminate hematogenously to different organs. After a variable incubation period, the disease manifests in two stages: an early stage that involves constitutional symptoms, arthralgia, headache, pruritus, and lymphadenopathy, and a late stage with predominant neurological symptoms and high mortality rates unless treatment is instituted. *T. b. rhodesiense* causes an acute or subacute syndrome that evolves over days to weeks, whereas *T. b. gambiense*, which represents 97% of HAT cases, causes a more protracted clinical course over months to years.

Cardiac manifestations are not a prominent feature of *T. brucei* but have been described for HAT. Studies looking at clinical aspects of HAT have focused mainly on central nervous system signs and symptomatology (38). Therefore, whether cardiac signs and symptoms in HAT are being overshadowed by predominant neurological involvement or whether their prevalence is truly low is an important question that remains unanswered.

(i) Epidemiology. In the 1960s campaigns to control the disease in areas of Africa where the disease is endemic had achieved a decrease in the prevalence of the disease to less than 0.1%. However, after many of these countries became independent, local governments failed to sustain existing programs or implement new ones. In the late 1990s, 60 million individuals living in 36 African countries were still exposed to HAT, and 30,000 to 40,000 people were contracting the disease every year (345). Furthermore, the yearly incidence in 1997 to 1998 paralleled that of the 1930s (299). This led to the strengthening of local programs in countries where the disease is endemic for the surveillance and control of HAT with technical and financial support from the WHO. As a result, the incidence of *T. b. gambiense* infection has been decreasing since the late 1990s, but this decrease has been less prominent for *T. b. rhodesiense*. However, *T. b. gambiense* infection remains a major public health problem in the Democratic Republic of Congo, Angola, and Sudan. As of 2006, these three countries were still reporting more than 1,000 new cases per year and represented 90% of the burden of *T. b. gambiense* infection in Africa (299). Of these countries, the Democratic Republic of Congo contributes 70% of the reported cases, with a prevalence of more than 70% in certain provinces; in these provinces, sleeping sickness is the largest cause of mortality (346).

Similarly, 89% of the total burden of *T. b. rhodesiense* infection is currently reported from two countries, Tanzania and Uganda (299).

(ii) Pathology and pathophysiology. Pancarditis can be evidenced in experimental infection with *T. brucei* by using different animal models (229, 258, 260). Early infiltration of different cardiac layers with lymphocytes and plasma cells is followed by the infiltration of macrophages and polymorphonuclear cells in more advanced stages of the disease. This cellular infiltrate, which is observed in all cardiac layers but predominates in the endocardium (258) or the subepicardial and perivascular locations, depending on the animal model studied (229), is associated with increasing numbers of trypanosomes in the interstitium as the disease progresses. However, an involvement of the myocardium with degeneration, necrosis, separation, and edema of muscle fibers is also prominent and can be severe (229, 258). Parasites in association with a cellular infiltrate can also be seen in all four cardiac valves as well as in the conduction system and lymphatic drainage system of the heart (229, 258, 260). In the pericardium, bloody fluid containing numerous trypanosomes and fibrin can be observed (229). Macroscopically biventricular dilatation and pericardial fat edema can be observed in the advanced stages of the disease (229).

Similarly, postmortem studies of humans reveal chronic pancarditis with lymphomononuclear cellular infiltration in 67 to 80% of autopsies performed looking for cardiac involvement (4, 259). This pancarditis can be severe for 10 to 20% of these cases (4, 259) and can be the cause of death. Epicarditis and degenerative changes along with cellular infiltration in the conduction system of the heart have also been described (259). Myocarditis with different degrees of severity is a prominent finding and is described almost invariably when cardiac involvement is present (4, 164, 257, 259). Focal, chronic, nonthrombogenic valvulitis that can affect all four valve types has also been reported for 20 to 30% of cases (4, 256, 259). However, in contrast to experimental animal models with *T. brucei* infection, parasites are usually not observed (164, 259).

The macroscopic appearance of hearts of patients who have succumbed to HAT has been reported to be normal except for occasional valvular fibrosis reported by one autopsy study (259). However, postmortem findings of fatal cases of HAT caused by *T. b. rhodesiense* do include increased pericardial fluid in 100% of cases and cardiomegaly in 33% of cases (164).

Data that correlate findings from postmortem studies indicating cardiac inflammation and associated degeneration and necrosis with a proinflammatory cellular phenotype to which such damage could be attributed are lacking. Thus, the immunopathogenesis of the early and late stages of HAT in animal models and humans has been studied without specific reference to cardiac pathology. During early HAT infection, B and T lymphocytes respond to variant surface glycoprotein (VSG) molecules (the immunodominant antigens that comprise the surface coat structure and cover the parasite plasma membrane), which results in antibodies to exposed VSG epitopes that efficiently clear the organisms from the blood (83, 188, 197). This coat of 10^8 VSG molecules constitutes the parasite's primary immune evasion strategy through antigenic variation by the continuous transcriptional switching of VSG genes (248, 326, 329). A single VSG gene is expressed at a time, from a repertoire of approximately 1,000 genes (21, 329). The switching rate can be approximately 1×10^{-3} switches per cell per generation (326). In addition, a type 1 cytokine response causes the release of IFN-γ (130, 292). IFN-γ activates tissue macrophages, which produce reactive nitrogen intermediates, reactive oxygen intermediates, and tumor necrosis factor alpha (TNF-α), which also destroy trypanosomes in the extravascular tissues (198). As stated above, despite the effective immune response, parasites can escape destruction through the antigenic variation of their VSG molecules, which enables them to perpetuate infection (44). Macrophages with a capacity to de-

press host T-cell proliferative responses to VSG and other trypanosome antigens are also generated by infection, allowing greater parasite survival (342).

Later in the course of infection, there are blood-brain barrier alterations that correlate with the presence of trypanosomes in the brain, neurological signs, and high levels of IgM in the cerebrospinal fluid (CSF) (35). How trypanosomes penetrate the barrier is not clear, but some authors suggested that the inflammation seen when trypanosomes become associated with the brain capillaries may be responsible for increased permeability (97). Once the parasites have invaded the CSF, a balance between proinflammatory and counterinflammatory responses may influence the outcome of CNS infection. IL-6, IL-8, TNF-α, and IL-10 levels have all been shown to be elevated in the CSF during late-stage disease (173, 190, 191). Proinflammatory cytokines play an important role in the neuropathogenesis of the meningoencephalitis seen in HAT, but counterinflammatory cytokines such as IL-10 downregulate the production of proinflammatory cytokines by astrocytes and microglia (307). Therefore, inflammation is initially regulated through the actions of these counterinflammatory cytokines, but this regulation abates in the terminal phases of the infection, leading to an overwhelming inflammatory response (308).

(iii) Clinical manifestations of heart involvement. Symptoms of heart failure during the end stage of experimental infection with *T. brucei* in dogs have been shown to correlate histologically with severe myocarditis and cardiac dilatation postmortem (229). In humans, signs of heart failure have also been reported during the late stages of fatal cases of *T. b. rhodesiense* HAT, where myocardial involvement has been proven by histology (85). Signs of cardiac enlargement and signs of volume overload such as crackles and peripheral edema were described for a small fraction of these patients during late stages of the disease (85). In a prospective study looking at signs and symptoms of heart failure in patients with *T. b. gambiense* HAT, dyspnea upon exertion, cough, palpitations, abnormal cardiac rhythms, heart murmurs, hepatojugular reflux, hepatomegaly, and peripheral edema were all more commonly seen in patients than in healthy controls (39). Moreover, all of these symptoms resolved with the treatment of HAT and without specific treatment for heart failure. However, only mild to moderate dyspnea upon exertion and hepatomegaly were significantly more frequent for HAT patients than for controls, and even these symptoms were seen for only 15 to 20% of patients. Furthermore, in that same study, levels of laboratory markers of heart failure such as NT-pro-BNP (N-terminal prohormone brain natriuretic peptide) were shown to be significantly elevated in HAT patients compared to healthy controls, but these markers did not correlate with signs or symptoms of heart failure except for hepatomegaly (39).

Patients in the late stage of HAT are also significantly more likely than healthy controls to have abnormal electrocardiograms (ECGs); only 22% of these patients have normal ECGs (39). Findings such as low voltage, P-R segment (P wave-to-R interval tracing of the ECG) depression, and repolarization changes can be seen for 31, 8, and 34% of patients, respectively, and are relevant to anatomopathologic findings since these findings suggest myopericarditis (39). These findings, however, do not correlate with laboratory markers of myocyte necrosis, such as elevated troponin levels (39). Prolonged Q-T (Q wave-to-T wave tracing of the ECG) intervals are also more frequently observed for patients than for controls and may impose an added risk of death due to uncontrolled ventricular arrhythmias (39). Interestingly, significant conduction abnormalities are not a prevalent ECG finding for HAT patients despite histological evidence of the involvement of the conduction system of the heart in both animal models and human autopsy studies (30, 39, 258).

(iv) Diagnosis. Diagnosis of HAT is performed by the identification of the parasite by direct microscopic examination of blood smears, lymph node aspirates, or CSF. Concentration techniques such as capillary tube centrifugation, miniature anion-exchange centrifugation, and quantitative buffy coat smears can be used to improve the sensitivity of the detection of the parasite in the blood (18, 215, 342). Different centrifugation techniques can be applied to increase the sensitivity of the detection of trypanosomes from both blood and CSF (215, 342). *In vitro* culture systems and inoculation of animals with human specimens to detect trypanosomes are also used for diagnosis (7, 342). Another direct method for parasite detection is PCR; however, despite good sensitivity and specificity, this method is still limited to research settings (63).

Even with the most sensitive methods, detection of the parasite requires at least 1 to 5 trypanosomes per ml of sample taken (342). Indirect methods to detect the parasite are therefore used in these cases. The card agglutination trypanosomiasis test (CATT), which detects antibodies against *T. b. gambiense* in the patient's blood, is highly sensitive and specific and yields results in 5 min (234). The reported sensitivity and specificity vary from 88 to 100% and from 94 to 97%, respectively (234, 250, 300, 324). The card indirect agglutination trypanosomiasis test (CIATT) is an indirect assay that detects circulating antigens in blood that are common to both *T. b. gambiense* and *T. b. rhodesiense*; it has also demonstrated high sensitivity and specificity in areas of endemicity (96 and 98%, respectively) (231). Other conventional serological methods can also be used, such as indirect hemagglutination, immunofluorescence, and enzyme-linked immunosorbent assay, but have limited use for field testing since results require more time and their performance and interpretation require trained personnel.

Determination of the disease stage is important for treatment purposes. CNS involvement, as ascertained by the presence of a CSF white blood cell count of $>5 \times 10^6$ cells/liter, a CSF protein level of >400 mg/liter, or the presence of trypanosomes in the CSF, defines the second or late stage of the disease (342).

Establishment of a diagnosis of HAT cardiomyopathy, however, is not as clear-cut. In general, a paucity of clinical signs and symptoms exists in reference to the prevalence of cardiac involvement found postmortem. Even when signs and symptoms are present, it is often difficult to establish their precise etiology given their lack of specificity and the multiple confounding comorbidities observed for these patients (anemia and probable treatment-induced cardiotoxicity, for example). ECG changes that might suggest myopericarditis (such as the ones detailed above) are more frequently found in HAT patients than in controls (31, 70, 325). However, the one prospective study that looked for cardiac involvement included only patients with late-stage HAT and followed up patients for 6 months only. Therefore, it is still unclear whether cardiac

involvement is present during early stages or whether the changes observed during late-stage HAT can evolve years later to an established cardiomyopathy.

Cardiac involvement can therefore be suspected for patients with HAT and ECG changes (specifically low Q-R-S voltage, P-R interval depression, and repolarization changes) and evidence of cardiac enlargement upon imaging or physical exam, specifically if treatment has not yet been instituted. Definite confirmation would require histological evidence of cardiac inflammation. An endomyocardial biopsy, however, should not be attempted since the risks are likely to highly outweigh the benefits of such a procedure.

(v) Treatment and preventive measures. *(a) Etiological treatment*. If untreated, infection with either form of *T. brucei* results in close to 100% mortality (65). Treatment is recommended for all patients and will vary according to the causative organism and the stage of the disease.

In the hemolymphatic stage of the disease (early stage), suramin is recommended for *T. b. rhodesiense* and pentamidine or suramin (as an alternative) is recommended for *T. b. gambiense*. For adults, suramin is given as a dose of 100 to 200 mg intravenously (i.v.), followed by 5 doses of 1 g i.v. throughout the course of 21 days, and for children, 20 mg/kg is given on days 1, 3, 7, 14, and 21 (214). Adverse reactions include anaphylactic shock, rash, neuropathy, fatigue, anemia, hyperglycemia, hypocalcemia, coagulopathies, neutropenia, transaminitis, and renal failure (171, 172). Pentamidine is given at a dose of 4 mg/kg per day for 7 days for both adults and children (214). Pentamidine has an efficacy comparable to that of suramin and is better tolerated overall; hypotension and hypoglycemia are the most commonly reported side effects (171, 172).

When the parasites have crossed the blood-brain barrier and caused CNS disease (late stage), melarsoprol (active against both subspecies) or eflornithine (active against *T. b. gambiense* only) is the recommended agent. Melarsoprol is given at a dose of 2 to 3.6 mg/kg per day, but the form of administration varies by the time of trypanosomiasis; a shortened 10-day treatment course has been approved for *T. b. gambiense* based on the results of a large nonrandomized clinical trial, but this regimen has not been proven for *T. b. rhodesiense* infection, where the recommended dosing scheme remains unchanged (2 to 3.6 mg/kg per day administered for 3 days and repeated every 7 days for a total of three times) (293). Eflornithine, whose efficacy is comparable to that of melarsoprol, is administered as a dose of 400 mg/kg per day over the course of 14 days. Serious toxicity can be observed with melarsoprol as acute reactive encephalopathy, which occurs in 5% to 10% of treated patients and can result in a case-fatality rate of approximately 50% (342). Overall case fatality rates with treatment are 3.6 to 5.7% for melarsoprol and 0 to 2.6% for eflornithine (19). The reactive encephalopathy and other less severe side effects such as fever, hypertension, macular rash, severe headaches, peripheral neuropathy, and tremor are also more frequently observed for patients receiving melarsoprol than for those receiving eflornithine (64). Additionally, treatment failures as high as 30% at 2 years have been observed with melarsoprol (171). On the other hand, eflornithine can cause seizures, diarrhea, and myelosuppression, and its administration is more complicated (64, 171).

Given the toxicities observed with these two agents, the complex dosing schemes, and treatment failures observed, other treatment options have been evaluated. A large, multicenter trial is under way to evaluate combination treatment with nifurtimox and eflornithine. Data analysis from one of the sites involved in this study is already showing promising efficacy and safety results with the obvious advantages of a simplified dosing regimen (4-fold-fewer eflornithine infusions) and a shorter treatment course (eflornithine at 400 mg/kg per day given intravenously every 12 h for 7 days plus nifurtimox at 15 mg/kg per day given orally every 8 h for 10 days instead of eflornithine at 400 mg/kg per day given intravenously every 6 h for 14 days) (264). Other combination treatments, such as melarsoprol and eflornithine or melarsoprol and nifurtimox, were investigated initially but not pursued further due to significant toxicity (263).

(b) Symptomatic treatment. Signs and symptoms of heart failure in patients with HAT are relatively mild and do not correlate with ECG abnormalities or with laboratory markers of LV dysfunction (pro-BNP). Furthermore, these nonspecific signs and symptoms usually resolve with the etiological treatment of HAT (39). Specific medical treatment for heart failure or symptomatic treatment for myopericarditis is therefore not usually necessary despite anatomopathological or ECG evidence of the latter.

Etiological treatment itself can induce ECG changes (39, 149). This has been hypothesized to be secondary to inflammation in the conduction system of the heart as a consequence of the host's immune response to the parasite and has led some authors to consider steroids for treatment-induced ECG abnormalities, specifically for the treatment of atrioventricular (AV) blocks (277). This approach, however, remains to be validated by clinical trials.

(c) Preventive measures. At the level of countries where the disease is endemic, prevention efforts have focused on systematic population screening in order to identify and rapidly institute treatment of cases (in order to reduce the human reservoir in the case of *T. b. gambiense*) and vector control (345). The WHO has developed guidelines for HAT surveillance in collaboration with countries where sleeping sickness is endemic (343).

HAT in travelers has been reported more commonly in association with *T. b. rhodesiense* than with *T. b. gambiense*, and epidemics have been reported to be associated with game park visits (147). The existence of a wild-animal reservoir for *T. b. rhodesiense* has long been demonstrated (125). For *T. b. gambiense*, both wild and domestic animals have also been shown to be capable of acting as reservoir hosts (73, 233). Therefore, avoidance of travel to foci of heavy infestations of tsetse flies within areas of endemicity, particularly if in close proximity to domestic or wild animals, is the best way to prevent the disease. If such travel cannot be avoided, wearing heavier fabrics in neutral colors and covering as much skin as possible are advised. No vaccine is yet available (224).

Other Parasites

Toxoplasmosis. (i) Epidemiology. *Toxoplasma gondii* is a worldwide zoonosis capable of causing several distinct clinical syndromes in immunocompetent and immunocompromised individuals. *T. gondii* is a parasite of members of the cat family,

with humans and other warm-blooded animals serving as intermediate hosts (90). Humans become infected by either the eating of undercooked meat, ingestion of contaminated water, fecal-oral transmission from feline feces, congenitally through transplacental transmission, blood transfusion, or transplantation (109, 137, 210, 211, 275, 286, 304). Meat for human consumption is not routinely inspected for *T. gondii* infection in the United States or elsewhere in the world (89). Human-to-human transmission does not occur, with the exception of mother-to-fetus transmission. The incidence of *T. gondii* antibodies increases with increasing age but does not vary between sexes. The prevalences of antibody titers vary considerably among geographic regions and within a given population. The overall seroprevalence among adolescents and adults in the United States was found to be 22.5%, with a seroprevalence among women of childbearing age (15 to 44 years) of 15%, using specimens collected by the third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994 (150). In the United States, *T. gondii* seropositivity among HIV-infected individuals varies from 10% to 45% and correlates with seropositivity in the non-HIV-infected population. In Western Europe and Africa, the seroprevalence among HIV-infected populations is approximately 50% to 78% (69, 358).

(ii) Pathophysiology. *Toxoplasma gondii* multiplies intracellularly at the site of invasion and may spread to distant organs by the invasion of lymphatics and blood. Tissue cyst formation occurs within the first week of infection and is responsible for latent infection. *T. gondii* resides intracellularly in phagosomes within macrophages and myocardial cells (136, 145, 288). The parasite is propelled by an actin-myosin-dependent gliding-motility mechanism and establishes intracellular vacuoles (227, 287). This remodeling prevents lysosome fusion, which leads to the intracellular survival of the parasite (151). The immune competency of the individual is the determining factor in the recrudescence of latent infection. Immunity in the immunocompetent individual persists for life. T cells, macrophages, and type 1 cytokines are crucial for the control of *T. gondii* infection. Defective production of IFN-γ and interleukin-12, possibly mediated by CD40 ligand, may play a role in the lack of containment of the infection (176, 309). Cytokine stimulation of macrophage production of reactive nitrogen intermediates was hypothesized to assist in the host control of established infection (43). Both host and parasitic genetics appear to be important for disease pathogenesis. Associations of HLA-DQ3 with the development of toxoplasmic encephalitis and the possible protective role of HLA-DQ1 suggest that host genetic factors contribute to the development of disease (50, 189, 311). In addition, population genetic analysis of *T. gondii* suggests clonal expansion, which may identify clinically relevant biological differences (298).

(iii) Clinical manifestations. The clinical expression of toxoplasmosis depends on the level of immunity in the human host (137, 210, 286). In immunocompetent patients, acute toxoplasmosis is most often asymptomatic, but latent infection can persist for life. Latent infection is due to cyst formation and may subsequently reactivate in immunocompromised persons (136, 208, 255, 288, 304, 335, 352). Among these populations, toxoplasmosis often presents in the form of encephalitis or chorioretinitis. Myocarditis has rarely been reported as a manifestation of acute toxoplasmosis. This manifestation may occur in isolation or as part of a broader clinical spectrum of illness. Pericardial effusion, constrictive pericarditis, arrhythmias, and congestive heart failure in patients with *T. gondii* myocarditis have been described (109, 208, 211, 255). In patients with AIDS, the heart is the second most commonly affected organ after the brain (136, 255). Prevalences vary according to various studies, and diagnosis is usually made postmortem since cardiac involvement is usually clinically silent or dominated by CNS manifestations (3). Approximately 12 to 22% of AIDS patients had evidence of endomyocardial involvement by *T. gondii* at autopsy. The prevalence of cardiac toxoplasmosis confirmed at autopsy in the era of highly active antiretroviral therapy has been reported to be less than 10% (136, 255). *Toxoplasma gondii*-associated myocarditis can also occur in transplant patients due either to reactivation or to *de novo* infection from a seropositive donor to a seronegative recipient (275, 304). Indeed, toxoplasmosis is the most commonly reported parasitic disease occurring after heart transplantation and may simulate organ rejection (109). Disseminated toxoplasmosis with associated myocarditis can lead to a fatal outcome if no prior prophylaxis is given to transplant patients (335, 352). The prevention of toxoplasmosis relies on the serological screening of donors and recipients before transplantation to identify patients at a higher risk of toxoplasmosis, i.e., seropositive hematopoietic stem cell transplant recipients and mismatched (seropositive donor/seronegative recipients) solid-organ transplant recipients. Prevention in those patients presently relies on prophylaxis, usually with cotrimoxazole (86).

(iv) Diagnosis. The diagnosis of toxoplasmosis relies on serology or the identification of tachyzoites in myocardial tissue (304, 335). There is considerable variation in the sensitivities and specificities of commercially available serological assays (349). IgG antibodies appear early, peak within 6 months of infection, and remain detectable for life. A negative IgG antibody test essentially rules out prior or recent infection of an immunocompetent host (12). IgM antibodies may persist for years after infection and should not be used as the sole diagnostic criteria for recent infection (40, 180). Antibody avidity testing has proven very useful as a marker of the timing of infection. The presence of a high avidity indicates that the infection occurred at least 3 to 5 months earlier. This test is most helpful during pregnancy, where additional evaluation and treatment depend on the timing of infection relative to pregnancy (55, 179). No single serological test is sufficient to support the diagnosis of acute or chronic toxoplasmosis, and the use of a reference laboratory is often required. Patients may have slight lymphocytosis, and hepatic transaminase levels may be slightly elevated. Otherwise, laboratory findings are not specific. Kean and Grocott first described a toxoplasmosis-like cysts in the myocardium in 1945, and Adams subsequently described fluctuating S-T (S-to-T interval tracing of the ECG) changes in a 15-year-old boy with glandular-type toxoplasmosis (5, 155). Endomyocardial biopsy has successfully identified the organism in heart transplant patients (127, 186, 335). Although uncommonly reported, the benefit of early and specific diagnosis with endomyocardial biopsy in the setting of heart transplantation likely outweighs the potential risks. Local necrosis with edema and an inflammatory infiltrate upon biopsy are typical (279). Myocardial abscesses have also been reported;

however, abscesses are not common pathological features of toxoplasmosis (3, 279). Parasites may also be detected by using DNA amplification techniques. The sensitivity with whole blood or buffy coat is 15% to 85% and appears most valuable for disseminated disease (16, 77, 93, 249). Performance characteristics vary by the timing of testing in relation to therapy, gene target, primers, and sample preparation (23, 93). PCR has been reported to diagnose *Toxoplasma* more frequently than histology of cardiac biopsy specimen samples in the transplant setting (138). PCR assays can be valuable in making this difficult diagnosis, and reference laboratories with experience with these assays should be utilized.

(v) Treatment. The treatment of choice is based on a combination of pyrimethamine and sulfadiazine or pyrimethamine and clindamycin (221, 352). Leucovorin should be given to all patients taking pyrimethamine. Combinations of pyrimethamine and azithromycin or atovaquone may be considered for patients intolerant to other regimens based on data from immunosuppressed patients. The combination of pyrimethamine and sulfadiazine is also a first-line treatment regimen during pregnancy. However, alternatives exist for those concerned about potential toxicity and teratogenicity, and treatment choice is influenced by the duration of pregnancy and documentation of fetal infection. Serological screening of organ donors and recipients before transplantation allows the identification of patients at the highest risk of toxoplasmosis and provision of prophylaxis for these individuals (86). The optimal schedule for the provision of trimethoprim (TMP)-sulfamethoxazole (SMZ) prophylaxis in the transplant setting has not been defined; however, this drug is often administered daily or three times a week. Prevention is important for seronegative pregnant women and immunodeficient patients. Prevention is accomplished through physician-patient education and prophylaxis prescription, where appropriate. Educational efforts should focus on the avoidance of contact with materials potentially contaminated with cat feces, the use of gloves when handling cat litter or gardening, washing of hands thoroughly after contact with raw meat, cooking of meat until "well done," and washing of fruits and vegetables before consumption.

Cysticercosis. (i) Epidemiology. Cysticercosis is a consequence of the ingestion of the eggs of the pork tapeworm *Taenia solium*. Cerebral cysticercosis is considered the most serious complication. The condition can also present as ocular, spinal, cutaneous, muscular, or cardiac lesions (182, 290). The prevalence of cysticercosis varies in countries where cysticercosis is endemic and is often increased in regions where pigs are raised and sanitary conditions are lacking (348). Few cases are acquired in the United States, and travel to areas of endemicity may pose a small risk to travelers (336).

(ii) Pathophysiology. Following egg ingestion, oncospheres invade the bowel wall and disseminate to the brain, striated muscles, and other tissues. Cysticerci can remain quiescent for many years in a state of immune tolerance. Poorly understood metacestode-elaborated substances divert the complement pathway and inhibit normal cellular immune responses, including macrophage function and lymphocyte proliferation (341). The ability of the cyst to moderate the host immune response may be lost with time (340).

(iii) Clinical manifestations. Clinical manifestations often develop at the time of cyst degeneration. The trigger for this event is unknown (340). The myocardial inflammatory response is variable, resulting in granuloma formation and fibrosis, which subsequently leads to arrhythmias and conduction abnormalities either spontaneously or during treatment (46, 181, 182, 290). Cardiac involvement in cysticercosis was thought to be rare, but autopsy studies have shown a prevalence of 20 to 25% in patients with concomitant documented neurocysticercosis (181, 182, 290). Cardiac cysticercosis is often asymptomatic and discovered during cardiac surgery or at autopsy. Cysticerci are usually multiple and randomly distributed in cardiac tissues, including the subpericardium, subendocardium, and myocardium (181, 182). Rarely, a single cardiac cyst may be present.

(iv) Diagnosis. The diagnosis is based on suggestive epidemiology and serology. The extent of diagnostic evaluation depends on the severity of clinical presentation. Routine blood tests may reveal marked peripheral eosinophilia only in the case of a leaking cyst. The sensitivity and specificity of serology vary with the site and stage of infection. An enzyme-linked immunoelectrotransfer blot assay is the test of choice for the detection of antibodies (111). PCR-based tests have an emerging role in the epidemiological investigation of taeniasis and are available for the diagnosis of cysticercosis (128, 212, 354). Most individuals with cysticercosis do not have viable *T. solium* in their intestines. Echocardiography may play some role in identifying cardiac cysts and occasionally identifies cardiac cysts consistent with cysticercosis upon routine screening for other purposes (32, 95). Cardiac magnetic resonance imaging (MRI) may also demonstrate cystic lesions, which are hypointense on T1-weighted images and hyperintense on T2-weighted images. Rounded scolices, when seen, are of intermediate to low signal intensity on T2-weighted images and of intermediate to hyperintense signal intensity within the low-signal fluid on T1-weighted images (68, 297).

(v) Treatment. Patients with extraneural cysticercosis should be evaluated with brain imaging for possible neurocysticercosis. Asymptomatic extraneural cysts may not require specific surgical or antihelminthic therapy. The role of albendazole and praziquantel or surgery in cardiac cysticercosis is unclear and has not been directly investigated; however, these therapies are likely to be effective given their efficacy at other sites (181, 182, 290). Adjunctive corticosteroids are sometimes administered during therapy for neurocysticercosis (82, 110). The potential benefit of decreasing treatment-related inflammation in cardiac cysticercosis has not been defined but remains theoretically possible.

Trichinellosis. (i) Epidemiology. Trichinellosis is caused by the nematode *Trichinella spiralis* and other *Trichinella* species and is common worldwide. Humans become infected when eating undercooked meat contaminated with cysts of *Trichinella* larvae (15, 170, 225). Approximately 15 cases of trichinellosis are reported annually in the United States (284). Wild carnivorous animals perpetuate infections in a sylvatic cycle, and wild-game meat is emerging as a source of infection (11, 62).

(ii) Pathogenesis. *Trichinella* larvae excyst and cross the small intestine, where they travel through lymphatics and the bloodstream until finally encysting in striated muscle tissue. The striated muscle cell is induced to transform into a nurse cell,

which supports the long-term viability of the encysted larvae (88). The process of encystment and nurse cell formation is unique to skeletal muscle and does not take place within the heart (92). *Trichinella spiralis*-associated myocarditis is not caused by the direct larval invasion of the myocardium with encystation but is likely induced by an eosinophil-enriched inflammatory response resulting in eosinophilic myocarditis similar to the pathogenic process associated with tropical endomyocardial fibrosis (71, 162, 303). Some patients with trichinellosis develop organ-specific autoantibodies, whose role in pathogenesis remains unclear (262).

(iii) Clinical manifestations. The clinical picture of trichinellosis is proportional to the number of larvae ingested and manifests with two clinical stages: the intestinal stage and the muscular stage (15, 170, 225). Larval migration into the muscles can cause periorbital and facial edema; subungal, conjunctival, and retinal hemorrhages; myalgias; weakness; and fever (71, 162, 303). The tropism of *T. spiralis* for striated muscle may involve the myocardium in 21 to 75% of infected patients (71, 162). Myocarditis is a consequence of migrating larvae and the resulting inflammatory response and typically occurs in the third week of infection. Trichinosis myocarditis may initially manifest with chest pain and mimic an acute myocardial infarction (162). Reports suggest that ECG evidence of myocardial involvement may be found for up to 75% of patients. Complications such cardiac arrhythmias are considered the most common cause of death associated with trichinellosis (71, 303). In addition, pericardial effusions have also been reported during *T. spiralis* infection (162).

(iv) Diagnosis. The clinical suspicion of trichinellosis is based on suggestive epidemiology associated with the typical clinical presentation and the presence of eosinophilia during the second to fourth week of the muscle stage (163). There is no direct relationship between the severity of eosinophilia and clinical course (163). Confirmation is based on serology and muscle biopsy specimens (170, 225). Serology is generally reliable and first becomes positive about 3 weeks after infection (230). Antibody levels may remain positive for longer than a year after clinical resolution. For patients without obvious myocardial involvement, some researchers have recommended screening with troponin to detect asymptomatic myocarditis (168). The finding of larvae in a muscle biopsy specimen provides a definitive diagnosis; however, biopsy is rarely necessary. ECG findings are considered nonspecific. In a study of 154 cases of trichinellosis, 56% of the patients had ECG abnormalities, most commonly nonspecific repolarization changes, without an association with poor prognosis (265). One study reported pericardial effusion as the most common cardiac manifestation of trichinosis, affecting 10% of patients (170). Cardiac MRI may provide supportive evidence of myocardial involvement, although the MRI findings are not specific to trichinellosis (156).

(v) Treatment. Treatment consists of the administration of albendazole or mebendazole in conjunction with steroids for severe cases (15, 71, 162, 170, 225). Although albendazole and mebendazole are relatively contraindicated in pregnancy, both have been used in patients without adverse fetal effects (120). Adjunctive steroids are commonly utilized for 10 to 15 days.

PARASITES THAT OCCASIONALLY INVOLVE THE PERICARDIUM

Entamoeba histolytica

Epidemiology. Amebic pericarditis is caused by the protozoon *Entamoeba histolytica*, which is transmitted by the fecal-oral route (143, 177). It has a worldwide distribution but is found mainly in developing countries in the tropics (251). In the United States, amebiasis is seen in immigrants and travelers returning from countries where the disease is endemic (54, 143, 160, 295). Following malaria and schistosomiasis, amebiasis is the third most common cause of parasitic death (337). Particular high-risk groups include children, pregnant women, and malnourished individuals (338). Invasive amebiasis may be more common among HIV/AIDS patients, prompting some to call for routine HIV testing of those diagnosed with the disease (67, 139, 140).

Pathophysiology. The ability of *Entamoeba histolytica* to invade tissues distinguishes it from the morphologically identical *Entamoeba dispar* (54). The parasite causes acute inflammation and ulceration of the colonic mucosa. Adherence to colonic epithelial cells using the Gal/GalNAc lectin is essential for amebic survival and pathogenicity (306). Mucosal IgA immunity to this lectin has been associated with protection from *Entamoeba* infection and disease in Bangladeshi children (122, 124). The trophozoite utilizes the secretion of proteinases for the dissolution of the extracellular matrix and the formation of amebepores resulting in target cell cytolysis, among other mechanisms, to establish its pathogenic niche (178, 218, 350).

Clinical manifestations. Extraintestinal amebic disease is localized mainly to the liver (143, 295). The involvement of the pericardium is very rare but is a serious complication of amebiasis (143, 295). Amebic pericarditis may present as either a pericardial rub with electrocardiographic changes associated with an abscess of the left lobe or purulent pericarditis from the perforation of the abscess into the pericardium (165, 166, 192). Amebic abscesses in the right lobe of the liver have also been reported to communicate with the pericardium (310, 339). The presenting clinical syndrome is usually one of two forms: (i) sudden onset as cardiac tamponade with chest pain, shortness of breath, and shock or (ii) progressive effusion with a slower course to develop fever, dyspnea, and pain (126, 223). Amebic pericarditis has been more frequently described for pediatric populations in which the association of concomitant intestinal amebiasis may be as high as 20% (143, 177).

Diagnosis. Diagnosis is usually established by serology, which has a sensitivity of about 90% (282). Infection with *E. histolytica* results in the development of antibodies, while infection with *E. dispar* does not. Positive serology does not distinguish between acute and past infections. For this reason, serum antigen tests are often used to complement diagnosis. The galactose lectin serum antigen is present in 75% of individuals with amebic liver abscesses (1). Peripheral eosinophilia is not particularly common (72). Stool microscopy has limited value for the diagnosis of extraintestinal amebiasis. Amebic cysts or trophozoites are detected in the stool only 15 to 33% of the time (8). In addition, the presence of amebic cysts or trophozoites determined by stool microscopy does not definitively indicate that the extraintestinal focus is secondary to the

identified intestinal parasite because both pathogenic and nonpathogenic *Entamoeba* may be present in the gut. However, an ELISA method can differentiate pathogenic from nonpathogenic *Entamoeba* in stool samples (121, 123). DNA amplification techniques for the rapid and specific identification of *E. histolytica* are in development (37, 48, 219, 357). Aspirated pus is usually sterile, and diagnosis should not be excluded based on its gross characteristics (296). Given the limitations of serology in the diagnosis of invasive amebiasis, PCR-based diagnostic methods have become an invaluable sensitive and specific tool for the diagnosis of intestinal and extraintestinal amebiasis and are available from many reference laboratories (37, 48, 121, 301, 357). The suppurative feature of amebic pericarditis may also cause it to be confused with tuberculous pericarditis (143, 295). A distinguishing factor between tuberculous pericarditis and amebic pericarditis is that there is a predominance of neutrophils in patients with amebiasis (143, 295). Imaging with chest computed tomography (CT) and echocardiography can be useful given the potential to demonstrate a liver abscess in continuity with the pericardium and fluid within the pericardial sac, with or without the fistulous tract (295).

Treatment. The treatment of pericardial amebiasis requires a combination of surgical drainage and metronidazole (177, 295). Metronidazole should be given three times daily for 7 to 10 days. Clinical improvement is expected within 48 to 72 h. If clinical improvement does not occur, bacterial superinfection should be considered and treated if found, and metronidazole therapy may be prolonged (53). Metronidazole resistance has not been reported (272). Treatment with a luminal agent to is required following therapy with metronidazole, even if prior stool examination was negative.

Echinococcosis

Epidemiology. Human infection with the metacestode form of one of the four species of the tapeworm *Echinococcus* (*E. granulosus*, *E. multilocularis*, *E. vogeli*, or *E. oligarthrus*) may result in echinococcal disease (9, 96, 157). *Echinococcus* species have a worldwide distribution. *Echinococcus granulosus* causes cystic echinococcosis, the form most frequently encountered. Humans become accidental intermediate hosts when they ingest eggs from the feces of infected dogs or other canids. Direct transmission from human to human does not occur.

Pathophysiology. After the ingestion of the eggs by an intermediate host, the eggs hatch and release oncospheres, which cross the small intestine and spread to encyst in various visceral organs. Both humoral and cellular immune responses to the presence of the oncospheres and metacestodes develop. The parasite evades the host immune response by using a number of mechanisms, including the cyst-laminated cuticle as a barrier to host cells, polyclonal activation of lymphocytes by parasite soluble antigens, and depression of host cell immune responses (315). For instance, chronic stimulation of the host by cyst fluid antigens leads to increased levels of specific IgG4 production, which is suggestive of host response immunomodulation (315). Th1 cell activation appears critical for protective immunity, while a Th2 response is correlated with progressive disease (276).

Clinical manifestations. Hydatid cysts develop over months to years. Most of them will remain asymptomatic, but some of them become large enough to cause symptoms (9, 157). Echinococcal disease is often diagnosed as an incidental finding during imaging for other reasons. Cysts are located mainly in the liver and the lung, and only 10% can occur in the rest of the body (96). Cardiac hydatid cysts have been described for 0.5 to 3% of echinococcosis cases and are usually univesicular (20, 47, 161, 185, 195, 241, 274, 319, 327). Clinical presentations of cardiac echinococcosis include arrhythmias, myocardial infarction, cardiac tamponade, pulmonary hypertension syncope, purulent pericarditis, and sudden cardiac death (20, 47, 185, 195, 241, 274, 319, 327). Isolated cardiac hydatid cysts without liver involvement are uncommon (20, 47, 319). Hydatid cysts can even mimic ST segment elevation myocardial infarction upon electrocardiography (100). Most cases of pericardial echinococcosis may be due to spread from an initial location at the liver dome (20, 47, 195, 327). Rarely, an atrial or ventricular thrombus may mimic a hydatid cyst (242, 302).

Diagnosis. Diagnosis relies on positive serological testing and radiographic findings (9, 96, 157). The sensitivity and specificity of serology in those patients with liver involvement are greater than 80% but less sensitive when echinococcal disease is isolated at other sites (34). Children and pregnant women more often have negative serology than other populations (33). The identification of antigens in cyst fluid or serum may also assist in diagnosis (246, 273). Fewer than 15% of cases have peripheral eosinophilia. DNA amplifications tests are not currently available outside the research setting. Echocardiography is the most appropriate imaging test to evaluate potential myocardial or pericardial hydatid cysts (183). CT imaging and MRI may also demonstrate specific signs, including the calcification of the cysts' walls, the presence of daughter cysts, and membrane detachment (94, 112).

Treatment. The drug of choice for the treatment of echinococcosis is albendazole or mebendazole (99, 114, 214). Mebendazole is usually continued for 3 to 6 months. Albendazole is preferred and is also used for 3 to 6 months (316, 321, 322). Antiparasitic therapy should be started at least 4 days before surgery and be continued for at least 1 month (albendazole) or 3 months (mebendazole) after surgery. Surgery, when feasible, is the most common form of treatment of echinococcosis (99, 114, 214). According to the WHO, surgery is not recommended for pregnant women, those with multiple or difficult-to-access cysts, or patients with dead or totally calcified cysts. Asymptomatic cysts, if heavily calcified and presumed nonviable, may be monitored without specific therapy. The routine use of a protoscolicidal agent during surgery is not necessary (153). The puncture, aspiration, injection, and respiration (PAIR) technique is an option for inoperable cysts (9). Patients should be on antiparasitic therapy prior to this procedure to reduce the risk of cyst dissemination. The response to specific therapy may be monitored with serology and imaging.

MISCELLANEOUS SYNDROMES

Schistosomiasis

Myocardial or pericardial involvement by *Schistosoma* species is a rare event and is due to the accumulation of *Schisto-*

soma eggs, which induce a local granulomatous response (66, 80, 196). However, chronic schistosomiasis may lead to severe liver fibrosis secondary to hepatosplenic involvement (84, 196). This process involving portal hypertension may produce a hepatopulmonary syndrome manifested as dyspnea upon exertion, right ventricular hypertrophy, and, ultimately, *cor pulmonale* (66, 80, 84, 196, 353). In addition, endothelial damage to the pulmonary circulation results from the shunting of *Schistosoma* eggs through portosystemic shunts. The ability of *Schistosoma mansoni* to survive during its residence in the pulmonary circulation is due to molecular masking by coating with ABO blood group glycolipids and major histocompatibility complex (MHC) molecules derived from the human host (66, 80, 196). *Schistosoma*-induced pulmonary hypertension carries a grave prognosis since it usually denotes an advanced stage of hepatosplenic schistosomiasis (66, 84). Thrombosis *in situ*, particularly of the right pulmonary artery, as well as cardiac arrhythmias and sudden cardiac death syndromes may occur (84, 196). The treatment of schistosomiasis (all species) is praziquantel or, alternatively, oxamniquine for *S. mansoni* (66, 80).

Myocarditis Associated with *Naegleria fowleri*

Naegleria fowleri is a free-living amoeba, which is well known to cause an acute, purulent, primary amoebic meningoencephalitis (PAM), often in previously healthy young individuals with a recent history of water-sport activity in rivers, lakes, or ponds (355). The disease process is usually confined to the central nervous system. One report in the literature, which reexamined an earlier case report of disseminated amebiasis, provided evidence of possible disseminated *N. fowleri* (87, 213). Several authors have described the pathological recognition of PAM-associated diffuse or focal myocarditis (59, 91, 144, 205). In the reported cases of associated myocarditis, clinical cardiac manifestations have been nearly universally absent. Additionally, amoebas have not been found in the heart tissue, making causal conclusions speculative. The diagnosis of PAM, when made premortem, is typically accomplished by direct wet-mount examination of the cerebral spinal fluid for trophozoite forms. *Naegleria fowleri* can be grown on agar plates coated with Gram-negative bacteria. Serological tests are not useful in the acute clinical setting given the delay in the mounting of a detectable immune response (187, 207, 247). A real-time PCR assay has been developed for *N. fowleri* identification and could become useful for fast laboratory diagnosis of PAM (266). To date, there are no reports of the use of this assay on myocardial specimens. Additionally, PCR-based diagnosis has been evaluated with formalin-fixed and paraffin-embedded brain sections (291). Amphotericin B remains the backbone of PAM therapy, and *N. fowleri* is highly susceptible to this drug *in vitro* (118). Successful therapy has been rare, and when reported, amphotericin B is usually part of the therapy (51, 294, 330). In a mouse model of PAM, azithromycin and amphotericin B have demonstrated synergistic success and may hold promise as combination therapy (305).

Zoonotic Filariasis

Dirofilaria immitis, a common parasite of dogs and other canids, is prevalent in many areas of the world and can occasionally affect humans. In the dog, the parasite undergoes its early development in the subcutaneous tissues for about 3 months before migrating to the right side of the heart. Once deposited by a mosquito vector, the adult worms live in vascular beds and can induce myocarditis (116, 240). Although adult *D. immitis* worms have been found in the heart and major vessels of humans at autopsy on several occasions (312), the usual finding is for immature worms to be located in partially or completely occluded small pulmonary arteries, where the obstruction has produced a distal pneumonitis followed by granuloma formation, resulting in a well-circumscribed coin lesion containing the parasite (6, 240, 320). These lesions are usually identified in asymptomatic individuals undergoing routine chest radiographs. No worms have been identified by echocardiography or angiography during premortem evaluation. Other filarial species, such as lymphatic-dwelling human filariae (*Wuchereria* spp. and *Brugia* spp.), may also be identified as pulmonary nodules (116, 240). The occurrence of severe, and occasionally lethal, myocardial involvement that often occurs in dogs and other canids has not been described for humans (116).

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia is a syndrome caused by a hypersensitivity response to microfilariae of the lymphatic-dwelling filariae *Wuchereria bancrofti* and *Brugia malayi* (235). This process, manifested as chronic pulmonary infiltrates with eosinophilia, may result in permanent deficits in pulmonary function (42). Clinical symptoms usually include cough, dyspnea, and nocturnal wheezing (332, 333). Eosinophils located in the lung, as a response to the presence of filariae in the pulmonary circulation, degranulate and lead to the production of toxic oxygen radicals that contribute to a chronic pulmonary inflammatory process (42, 280). These restrictive pulmonary function deficits may result in pulmonary hypertension that subsequently contributes to *cor pulmonale* (42, 235, 280, 318). The treatment of choice recommended by the WHO is the oral antifilarial drug diethylcarbamazine (DEC) for 3 weeks (333).

Tropical Endomyocardial Fibrosis

Helminth-induced hypereosinophilia has been associated with tropical endomyocardial fibrosis. The exact etiology of this entity remains unknown. Filariae and schistosomiasis are the nematodes most frequently found to induce chronic eosinophilia with consequent endomyocardial fibrosis (26, 267). The proposed immunopathogenesis suggests that when eosinophilia is persistent, blood eosinophils many undergo characteristic changes that have been associated with cellular activation and eosinophil-induced tissue damage (238, 267). This results in endomyocardial fibrosis, which is manifested clinically as restrictive cardiomyopathy (267). The clinical presentations of tropical endomyocardial fibrosis are similar to those of the idiopathic hypereosinophilic syndrome involving the heart (26, 238, 267). This process leads to endomyocardial fibrosis, mural thrombus formation, arrhythmias, and pericarditis with effusion in some cases. Echocardiographic criteria are utilized to diagnose endomyocardial fibrosis, and magnetic resonance imaging (MRI) may have a supportive emerging role (25, 102). A

tailored, individualized approach of combined surgical and medical therapy is the optimal plan of care (220). Prognosis is poor, and death often results from complications of chronic heart failure and its associated morbidities.

Visceral Larva Migrans

Visceral larva migrans (VLM) is caused primarily by infection with *Toxocara canis* and less frequently by *Toxocara catis* or *Baylisascaris procyonis*. The syndrome is characterized by eosinophilia, fever, and hepatomegaly (24). In the United States, seropositivity to *Toxocara* has ranged from 2.8% in an unselected population to 54% in a highly selected rural population (115, 152). Similar to noncardiac manifestations, cardiac VLM has presented predominantly in children. Although almost any organ can be affected, the liver is the organ most frequently involved. Eosinophilia is a hallmark of the disease. Cardiac manifestations have included endomyocarditis, cardiac pseudotumor, and cardiac tamponade (45, 78, 81, 129, 331). The diagnosis can be definitively confirmed by finding larvae in the affected tissue by histological examination. *Toxocara* antibody titers vary by the population studied, as mentioned above, and may not be useful in definitively establishing the diagnosis. Many patients recover without therapy, and no single agent has been proven to be particularly effective. However, in the setting of severe cardiac disease, treatment with albendazole, mebendazole, or thiabendazole could be tried. Clinical vigilance must remain high for the possibility of a treatment-provoked inflammatory response that may respond to corticosteroids.

Sarcocystis Species

Sarcocystis is a zoonotic coccidian protozoal parasite. More than 120 species of *Sarcocystis* have been reported. Humans may serve as definitive hosts for pork and cattle *Sarcocystis* when ingested with poorly cooked or raw meat (175). Southeast Asia is the source of most human case reports (154, 351). In ethnic groups that routinely consume undercooked pork or beef, the prevalence has been reported to be up to 22% (154, 356). Most individuals are asymptomatic. However, clinical manifestations can include myalgia, fever, transient pruritic rashes, lymphadenopathy, and subcutaneous nodules associated with eosinophilia and elevated creatinine kinase levels (244, 328). Myocardial involvement has been suggested for a case presenting with cardiac conduction abnormalities (17). Serology is highly specific, and muscle biopsy may be useful for individuals with symptoms (146). No specific treatment for *Sarcocystis* is known, although albendazole was reported to suppress human symptoms (17).

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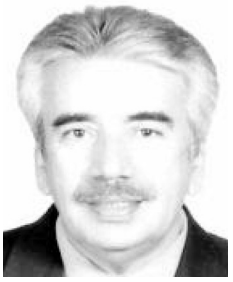

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